What Do We Look For To Support Pediatric Dosing?

Lily Mulugeta, Pharm.D
Pediatric Clinical Pharmacology Staff
Office of Clinical Pharmacology

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Outline

- Lessons learned from pediatric trials
- Dose selection and the Pediatric Decision Tree
  - Full extrapolation
  - Partial extrapolation
  - No extrapolation
- General considerations
  - Pharmacodynamic endpoints
  - Designing pediatric pharmacokinetic studies
  - Sequential versus parallel conduct

Lessons Learned

- Previous approach: "Pharmacokinetic studies in the pediatric population should determine how the dosage regimen should be adjusted to achieve approximately the same level of systemic exposure that is safe and effective in adults."

  1998 Draft FDA Guidance for Industry: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products

- Lessons learned from completed trials: Poor dose selection contributes to pediatric trial failures.
  - Antihypertensives (Benjamin et al. *Hypertension* 2008)
  - Drugs for neurogenic bladder dysfunction (Momper et al. *J Clin Pharm* 2014)
  - Clopidrogel (Plavix) for prevention of shunt thrombosis (Plavix FDA Clinical Review; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/020839Orig1s051SumR.pdf)

Lesson 1: Matching adult exposures is not always the best approach.

- Antihypertensives trials (Benjamin et al. *Hypertension* 2008)
  - Evaluated dosing for 6 pediatric trials: 3 successful and 3 failed trials
  - Major findings related to dose selection:
    - Failed trials did not investigate dose ranges higher than corresponding adult doses; 1 trail used fixed doses across a wide range of body weights (>5 fold range in BW)
    - Successful trials used a wide range of doses and adjusted for BW
- Drugs for neurogenic bladder dysfunction (Momper et al. *J Clin Pharm* 2014)
  - Reviewed 4 development programs : 2 anti-muscarinic, 2 alpha-1 antagonists)
  - All 4 programs targeted exposures seen in adults with overactive bladder or in treatment of BPH
  - No dose response seen in the studies
  - Major findings related to dose selection:

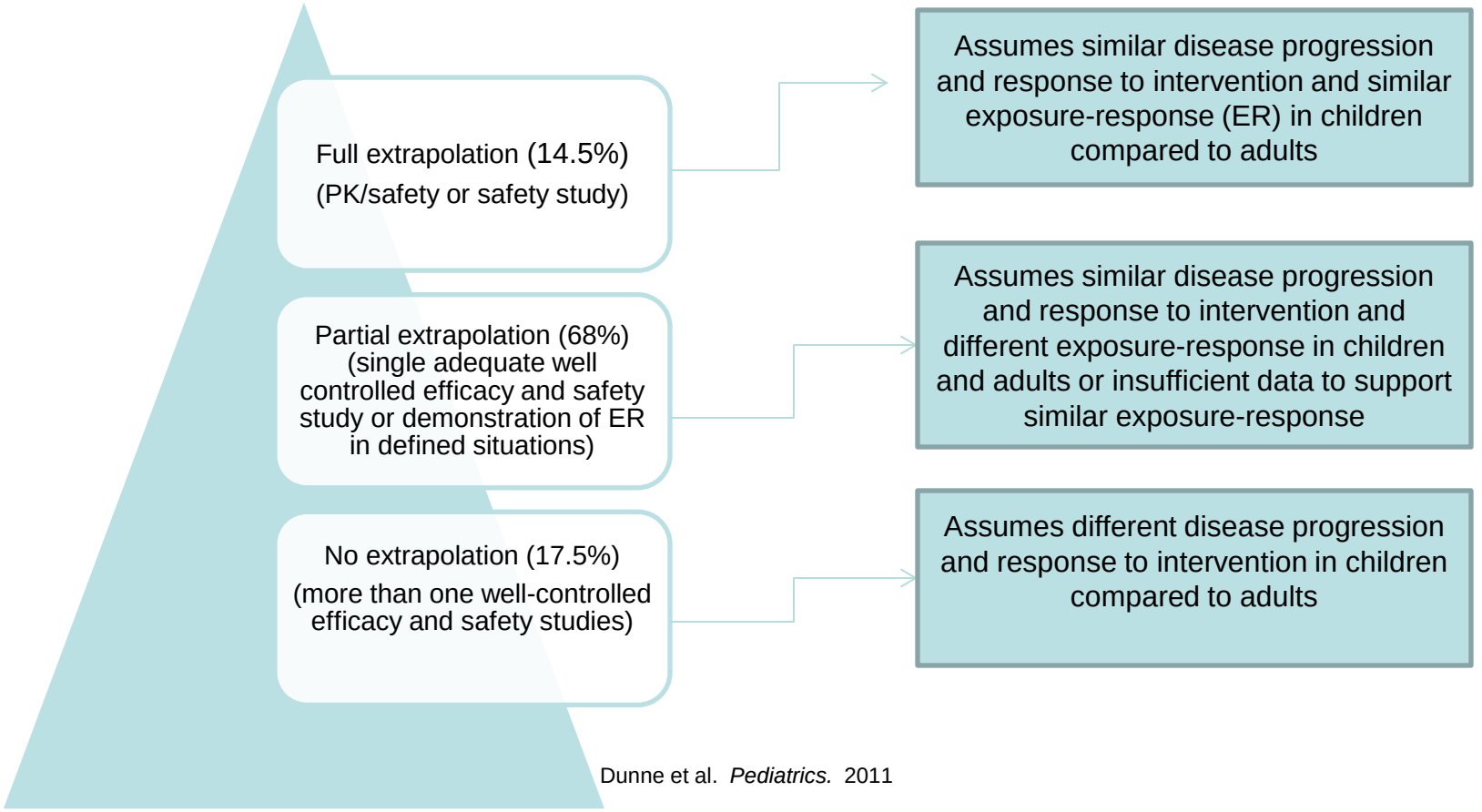
    "It is possible that if higher doses than those studied had been evaluated in the pediatric NBD drug development programs, efficacy may have been demonstrated."

Lesson 2: Matching adult PD effect is not always the best approach.

- Plavix for prevention of shunt thrombosis
  - Study 1: Dose ranging study in neonates and toddlers "at risk for thrombosis"
    - Objective: To identify a dose with similar relative reduction in PD effect after standard dose of Plavix in adults.
    - Study showed: Difference in PD at baseline in infants and toddlers compared to adults
  - Study 2: Randomized, double-blind, placebo-controlled trial in infants
    - Trial failed to demonstrate effect on the primary efficacy outcome
    - The dose selection was not well-supported; the dose was only 20% of the standard adult dose

Dose selection and the Pediatric Decision Tree

Dose selection depends on studies required to bridge adult & pediatric data.



Dunne et al. *Pediatrics.* 2011

Full Extrapolation of Efficacy

- Appropriate when sufficient data on similarity (disease, response, ***and*** ER) between adults and children
- PK in relevant age groups to identify dose
- Simulations to identify a dose expected to achieve an appropriate target exposure for PK study(e.g., the observed adult drug exposure)
- Careful consideration should be given to:
  - Identifying key PK parameter(e.g. Cmax, Cmin, AUC…)
  - Acceptance boundary used to match exposures
- Pediatric-formulation related challenges
  - Differences in bioavailability (adult and pediatric formulation)
  - Dosing accuracy/flexibility
- Examples: anti-infectives, analgesics (down to 2 yrs)

Case Example: Full Extrapolation

- Zosyn (piperacillin/tazobactam); Approved in adults for tx of mod to sev infections by susceptible specific microorganisms
- PK study to derive dosing to match adult exposures:
  - Open label, ascending single dose PK /safety study of 2 fixed doses in children ages 2 mos-12 yrs.
  - 6pts/age group; 2-5 mos, 6-23mos, 2-5 yrs, 6-12yrs
- Open label safety study in 542 patients
- Pop PK analysis:
  - Clearance for 9 mos-12 yrs comparable to adults (renally excreted)
  - Clearance 80% of adult in 2-9mos.
- Regulatory outcome: Zosyn approved at doses of
  - 100mg/12.5 per kg q8h in patients 9mos and older
  - 80mg q8h per kg in patients 2-9 mos

Partial Extrapolation of Efficacy: PK/PD trials

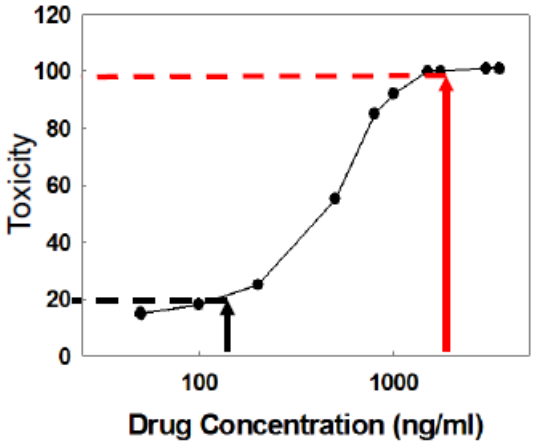
- Disease and response are believed to be similar but the ER in pediatric patients is inadequately defined.
- PD endpoint should be linked to clinical outcome
- Dose range should account for observed differences in response between adults and the pediatric population
  - May require exposures > approved adult dose (exposure) provided that ER and safety data justify such an exposure
- Distinctly different ranges of exposures are desirable for ER analysis and dose optimization
- Modeling & Simulation (M&S) should be used to support initial dose selection, sample size and sampling scheme for PK and PD
- Examples: sedation, anesthesia

Partial Extrapolation of Efficacy: Single Efficacy trial

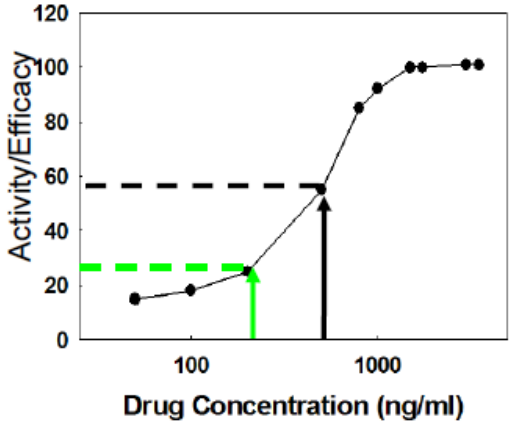
- Dose-ranging study with appropriate biomarker or clinical endpoint to select dose range for the efficacy trial or dose ranging within the efficacy trial
- May require exposures > approved adult dose (exposure)
  - M&S to support initial dose selection in some age groups
  - PK in initial cohort in age groups where most noticeable difference in PK is expected
  - For drugs *with known exposure-related safety signal,* PK study may be needed in all age groups
- Sparse PK sampling for ER analyses for effectiveness in efficacy trial to optimize pediatric dosing
- Example: schizophrenia, migraine, hypertension, type 2 diabetes

Use of Dose-Response Information in Selecting Doses

- Dose selection depends on shape and location of dose-response curve for both response and toxicity
  - Large separation between response and toxicity: Doses on or near plateau of the effectiveness dose-response curve
  - Small separation between response and toxicity: Doses lower on dose-response curve
- Doses should ensure adequate spread of attained concentration-response values and diminish overlap between attained concentrations
- For drugs with high PK variability, a greater spread of doses may need to be considered



Increased toxicity, as indicated by the red line



Reduced effectiveness, as indicated by the green line

Case Example: Partial Extrapolation

Palonosetron (Aloxi) 5HT3 antagonist for chemotherapy-induced nausea and vomiting (CINV)

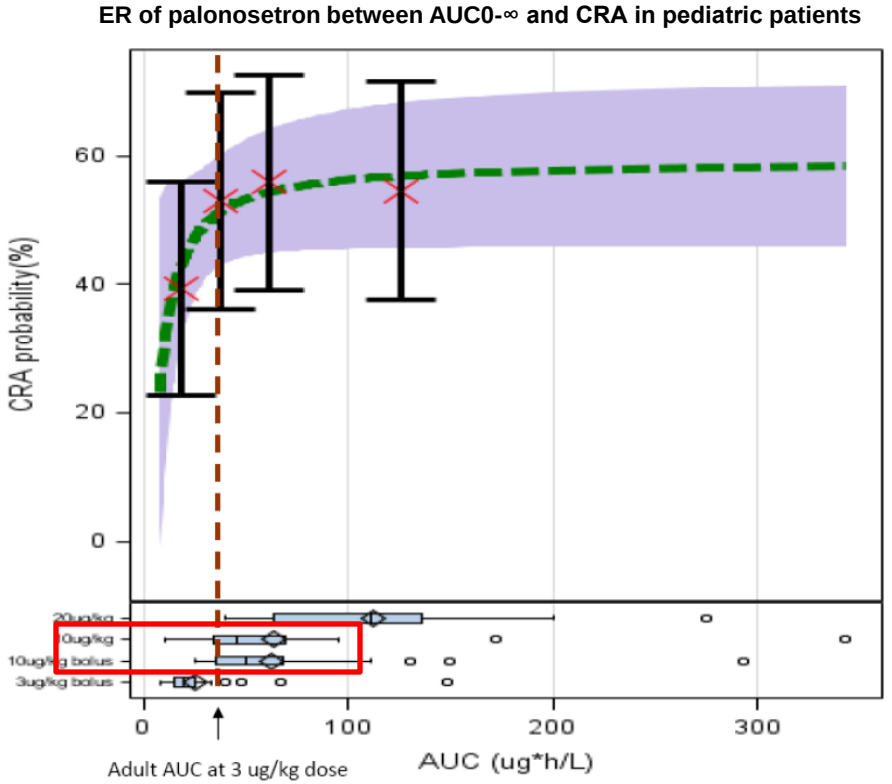
- Large separation between response and toxicity in adults

Pediatric Study 1: Phase 2 dose-ranging 0-17 yrs

Dose	Total N	% complete response
3mcg/kg	35	37.5
10mcg/kg	37	54.1

- Dose response for CR
- FDA: 10mcg/kg & 20mcg/kg for Phase 3 trial
  - Treatment effect at 10mcg/kg lower than adults
  - Diminish overlapping concentrations

Pediatric Study 2: Phase 3 non-inferiority (NI) trial to ondansetron 0-17 yrs



FDA approved 20mcg/kg down to 1month:

- Only 20 mcg/kg met NI margin
- No new safety signal
- Dose supported by ER for efficacy

No Extrapolation of Efficacy: Full Development

- Disease process unique to children, its progression undefined or dissimilar to that in adults, **and** no pertinent biomarker to predict effectiveness
- One or more clinical efficacy studies usually evaluating more than one dose
- The approach for dose selection similar to dose selection in partial extrapolation with a single efficacy study
- Only 34% result in a pediatric indication compared to 61% when partial or full extrapolation
- Examples: Major Depressive Disorders (MDD), ADHD

Case Example: No Extrapolation of Efficacy

- Under development for treatment of MDD in adults
- 2 required pediatric studies
  - Many failed trials both in adults and pediatric patients
- Sponsor proposed 2 clinical studies:
  - Study 1: Safety and Efficacy (12-17 yrs.); 2 flexible levels
  - Study 2: Safety and Efficacy (7-17 yrs.); 2 fixed dose levels
- Sponsor proposed the use of Pop-PK modeling to derive doses for the safety and efficacy studies and PK sampling in clinical studies
- Regulatory action: The Agency agreed given the age group to be studied; model prediction will be confirmed in 12-17 yrs. prior to enrolling 7-12 yrs

General Considerations

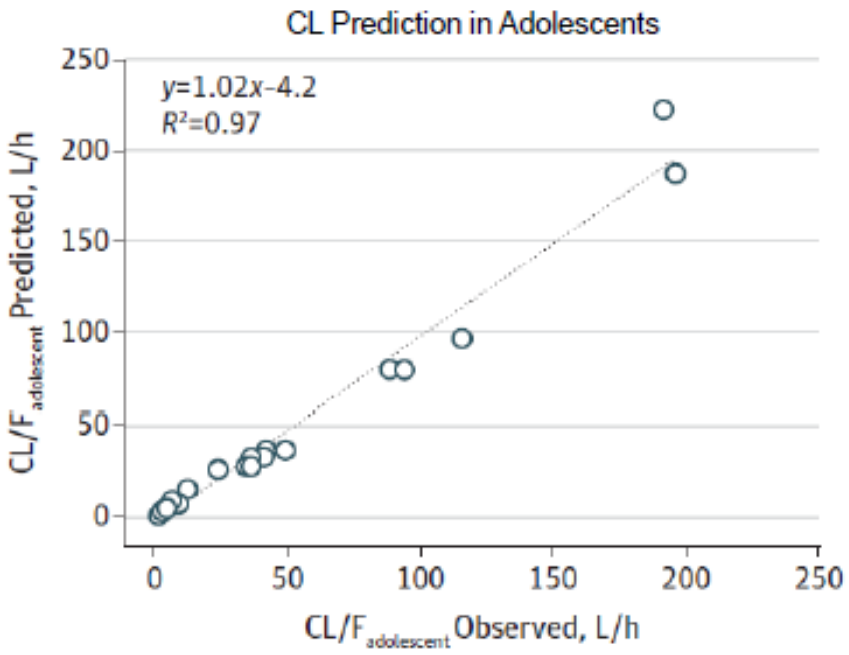
Pharmacokinetic Studies

- PK trial design should depend on the objective(s) of the trial and the ***scientific question***(s) to be answered.
- Age stratification should be based on developmental changes affecting PK/PD and safety
- Sample size of the study should be justified
- Methods of drug administration (e.g. with formula, apple sauce, crushed, etc..) and impact on PK should be considered
- Bioavailability of the pediatric formulation should be characterized
- Blood volume limits (especially in infants/neonates): need for sensitive/microvolume assays and use of sparse sampling

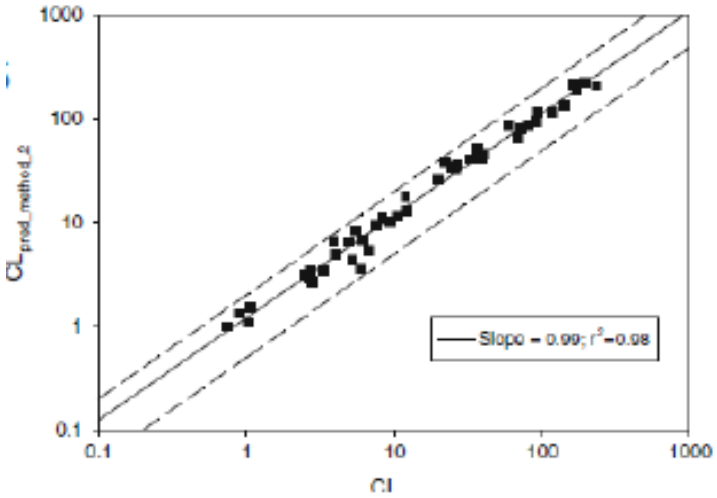
Separate PK studies should be considered on a case by case basis

- PK for some drugs may be reasonably predicted in children > 2 years using allometric scaling
  - Depends on available data on organ maturation
  - Proposed approach to bridging adult and pediatric data
  - Known/potential safety concerns
- For drugs with wide therapeutic windows
  - PK prediction using allometry maybe sufficient for dose estimation in some pediatric age groups
  - Sparse sampling in efficacy/safety study: maximizes therapeutic benefit to pediatric patients
- Greater emphasis on:
  - Age groups where PK can not be reliably predicted
  - Exposure response data for safety and efficacy

Allometric Scaling Predicts CL in Pediatric Subpopulations

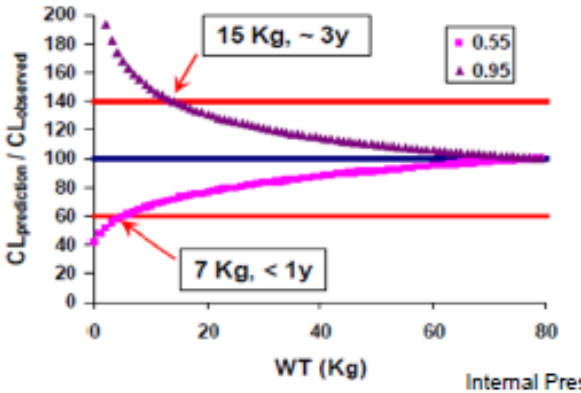


Momper et Al. *JAMA Pediatrics* 2013



Edington et Al. *Clin Pharm* 2013

Prediction trend of 0.75± 0.20



Internal Presentation by Yunzhao Ren April 2013

Sequential vs Parallel Conduct of Studies

- The best practice is not to always begin with adolescents and gradually move lower in age (sequential conduct):
  - Sequential conduct contributes to lag in pediatric drug development
  - Justified when specific safety concern/need for specific data from an older age cohort that precludes the use of parallel conduct
  - When sequential conduct of studies is necessary, separate cohorts rather than separate trials should be considered

- In the presence of adult data, sparse PK sampling (population PK) can be used when feasible to address ethical constraints

Pharmacodynamic Endpoints

- PD target linked to clinical outcomes most appropriate for pediatric dose selection
- Yet, few validated PD endpoints in pediatric patients (especially infants and neonates)
- ER approach may require validation studies for the PD endpoint (e.g. pain score in children)
- Limited data on age related differences in PD
- Limited data on influence of pediatric disease status on PD

Conclusion

- Pediatric dose selection should be depend on types of studies required to bridge adult and pediatric data.
- Available data (both adult and pediatric) should be leveraged to optimize pediatric studies.
- Pediatric dose ranges should account for observed differences in PK, PD, and/or clinical response between adults and the pediatric.
- Greater emphasis should be placed on exposure response data for efficacy and collecting PK in age groups where PK prediction is not reliable.

Back-up slides

Population Pharmacokinetics

- Quantitative approach to describe PK data
- Identifies sources of variability in Cl and Vd (e.g. age, body weight, organ function, etc…)
- Allows use of unbalanced and sparse sampling (2-3 samples/patient) versus dense sampling (>6 samples/patient)
- Commonly used for pediatric dose selection for trials and dose optimization
- Relies on assumptions to derive model
- Requires careful consideration of sample size and sampling scheme

Useful Resources

- ICH-E4: Dose-Response Information to Support Drug Registration
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E4/Step4/E4_Guideline.pdf
- ICH Topic E 11: Clinical Investigation of Medicinal Products in the Paediatric Population
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf
- FDA guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biologic Products (draft to be released soon)
- FDA Guidance for Industry: Population Pharmacokinetics (under revision)
- 2014 EMA Guideline on pharmaceutical development of medicines for paediatric use
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf